Biospecimen-Based Assessment Modalities Pathway Example

Sunday, November 9, 2008

Biomarker Pathway:

Biomarkers in Breast Cancer

Co-Chairs: Joe Gray, Richard Cote
Advocate co-chairs: Cindy Geoghegan and Ginny Mason

Biomarker pathway

Creation of Modality

Development of the test

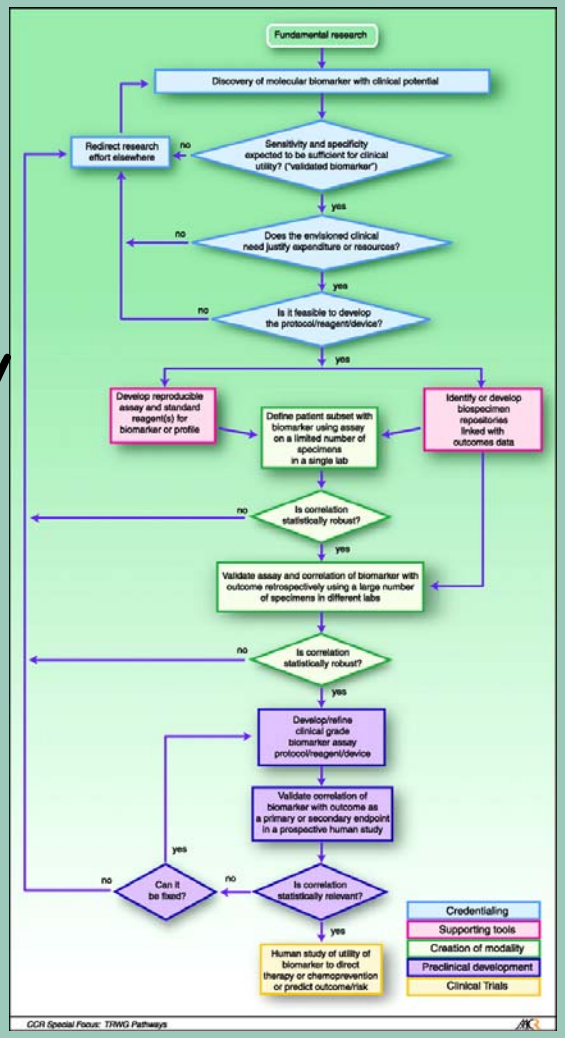
Validation in a retrospective study

Independent lab validation

Preclinical Development

CLIA assay

Prospective validation



Credentialing

Clinical need

Scientific validation of biomarker

Resources

Specimens for

- discovery
- retrospective validation
- prospective validation

Srivastava, S. et al. Clin Cancer Res 2008;14:5672-5677

AACR Clinical Cancer Research

Biomarker pathway

Macleod — BNIP3, prognosis
Niederhuber — Wound microenv, prognosis
Patsialou — Stroma and migration, prognosis

Norton — Tumor self seeding, prognosis

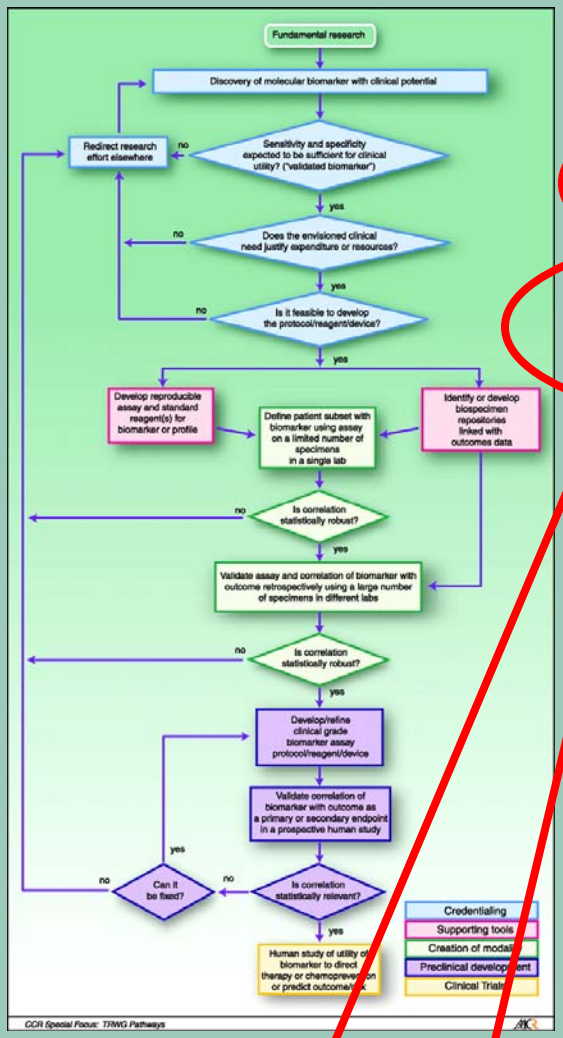
Clawson — CTC detection, prognosis
Yu — 14-3-3-zeta, in ADH, prognosis
Cote — CTC detection, prognosis
Oesterreich — E2-IGF interaction, prognosis

Tlsty — DCIS markers, prognosis
De Michele — IL6 SNP, prognosis
Chang — Stem expression, prognosis

Ellis — PALM50, prognosis

Thorner — b-Myb, prediction

Richardson Phase II, prediction



Srivastava, S. et al. Clin Cancer Res 2008;14:5672–5677

Fisher — MS and AS, early detection

Sukumar — QM-MSP, risk
Kahn — NAF estradiol, risk
Gray — in vitro predictors, prediction

Glass — CBCTR, resource
Paik — NSABP, resource

Kristal — Caloric restriction, risk
Atkinson — Daidzein-Metaboli. Phenotypes, risk
Smith — Phosphatase 2A, risk

Kummel — Surgical margins, prognosis
Iglehart — 8q22, prognosis

Keyomarsi — CCNE, prognosis

Couch — BRCA, risk

Early Resource

Clinical Cancer Research

Biomarker pathway

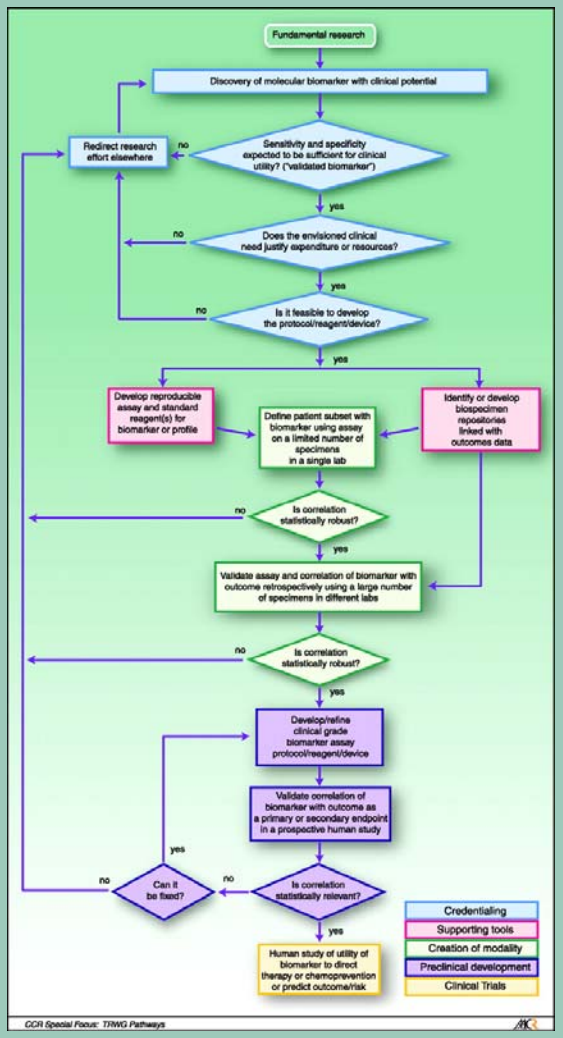
Macleod — BNIP3, prognosis
Niederhuber — Wound microenv, prognosis
Patsialou — Stroma and migration, prognosis

Norton — Tumor self seeding, prognosis

Clawson — CTC detection, prognosis
Yu — 14-3-3 zeta, DCIS, prognosis
Cote — CTC detection, prognosis
Oesterreich — E2-IGF interaction, prognosis

Tlsty — DCIS, prognosis
De Michele — IL6 SNP, prognosis
Chang — Stem expression, prognosis

Ellis — PALM50, prognosis
Thorner — b-Myb, prediction
Richardson Phase II, prediction



Fisher — MS and AS, early detection

Sukumar — QM-MSP, risk
Kahn — NAF estradiol, risk
Gray — in vitro predictors, prediction

Glass — CBCTR, resource
Paik — NSABP, resource

Kristal — Caloric restriction, risk
Atkinson — Daidzein-Metaboli. Phenotypes, risk
Smith — Phosphatase 2A, risk

Kummell — Surgical margins, prognosis
Iglehart — 8q22, prognosis

Keyomarsi — CCNE, prognosis

Couch — BRCA, risk

Srivastava, S. et al. Clin Cancer Res 2008;14:5672–5677

Circulating tumor cells

AACR American Association for Cancer Research
Clinical Cancer Research

Biomarker pathway

Macleod — BNIP3, prognosis
Niederhuber — Wound microenv, prognosis
Patsialou — Stroma and migration, prognosis

Norton — Tumor self seeding, prognosis

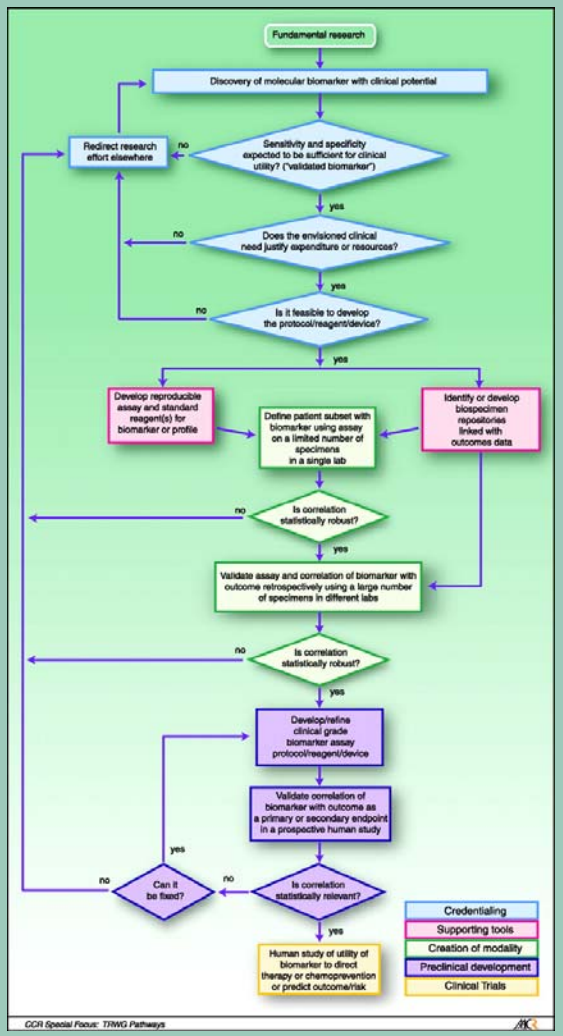
Clawson — CTC detection, prognosis
Yu — 14-3-3-zeta, DCIS prognosis
Cote — CTC detection, prognosis
Oesterreich — E2-IGF interaction, prognosis

Tlsty — DCIS, prognosis
De Michele — IL6 SNP, prognosis
Chang — Stem expression, prognosis

Ellis — PALM50, prognosis

Thorner — b-Myb, prediction

Richardson Phase II, prediction



Fisher — MS and AS, early detection

Sukumar — QM-MSP, risk
Kahn — NAF estradiol, risk
Gray — in vitro predictors, prediction

Glass — CBCTR, resource
Paik — NSABP, resource

Kristal — Caloric restriction, risk
Atkinson — Daidzein-Metaboli. Phenotypes, risk
Smith — Phosphatase 2A, risk

Kummell — Surgical margins, prognosis
Iglehart — 8q22, prognosis

Keyomarsi — CCNE, prognosis

Couch — BRCA, risk

Srivastava, S. et al. Clin Cancer Res 2008;14:5672–5677

DCIS Prognosis

AACR Clinical Cancer Research

Biomarker Pathway:

Markers to predict subsequent events in women with early breast cancer

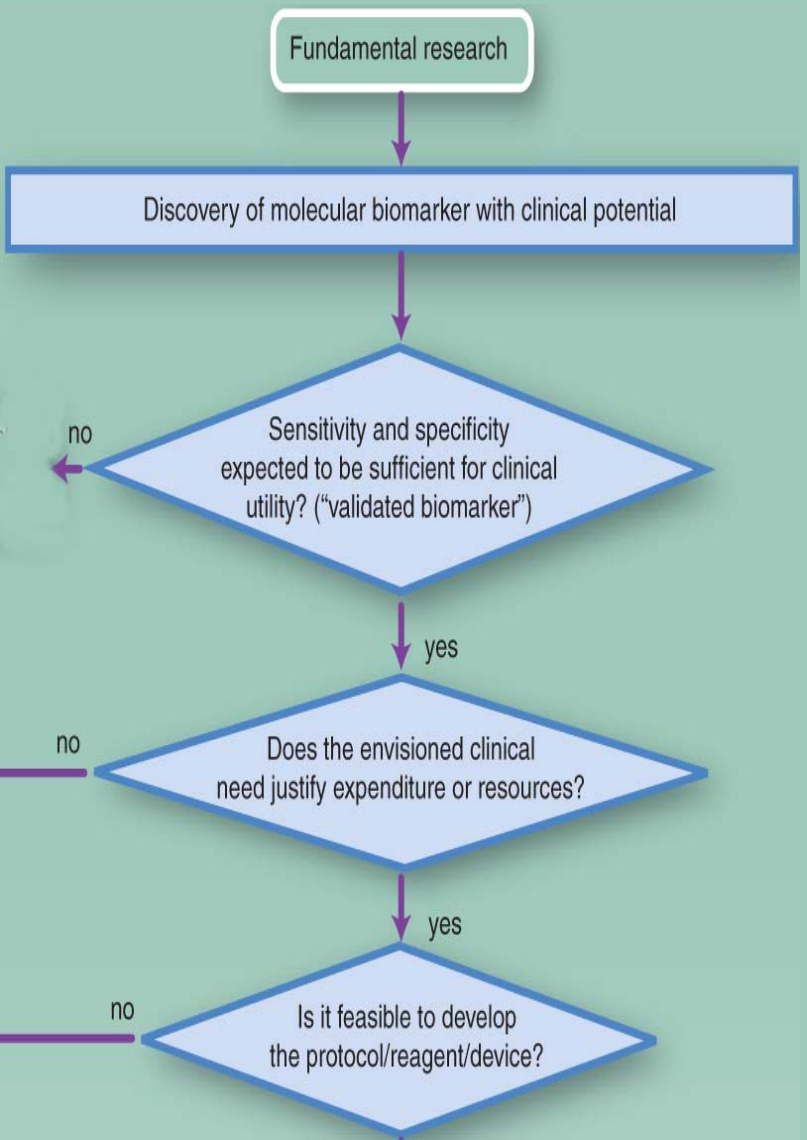
Abstracts

Tlsty et al, Biomarkers to Predict Subsequent Tumor Events in Women Diagnosed with DCIS

Yu et al, 14-3-3ζ in the Early Stages of Breast Cancer Progression: Luminal Filling and Epithelial Mesenchymal Transition

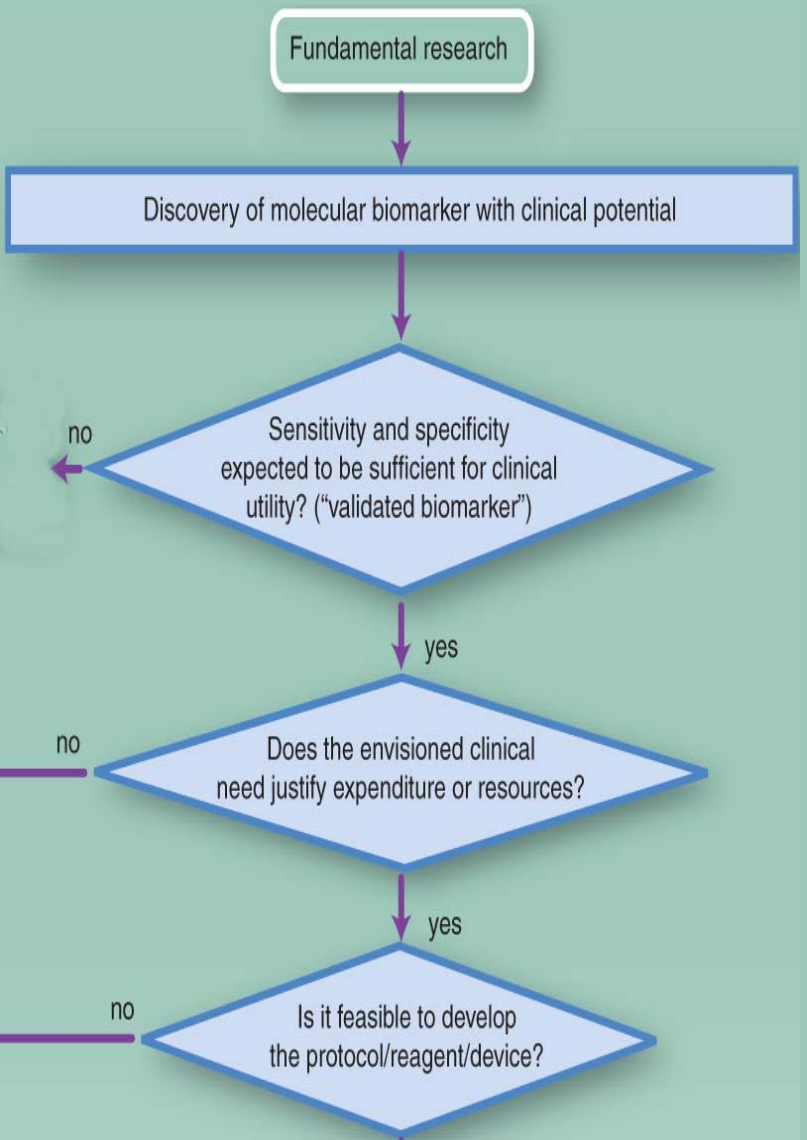
Almost every SPORE has a DCIS prognosis project!

Biomarker Pathway:
Credentialing: Clinical need



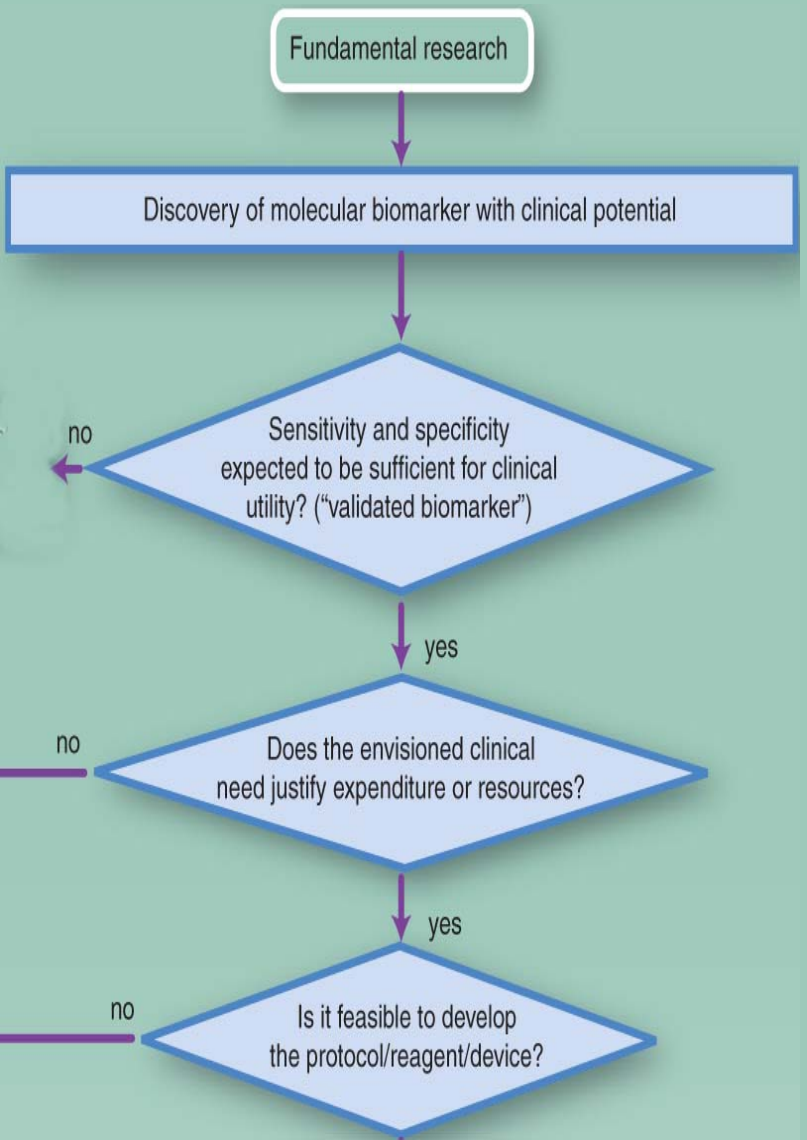
- DCIS rate increased by widespread application of mammographic screening
- 15%–30% of women with DCIS recur within 10yr
- 5 to 10% of DCIS cases progress to invasive cancer within 5 years
- A similar proportion recur as DCIS
- Most will not progress but are aggressively treated
- Molecular markers are needed to tailor treatment to risk

Biomarker 14-3-3ζ:
Credentialing: Scientific validation



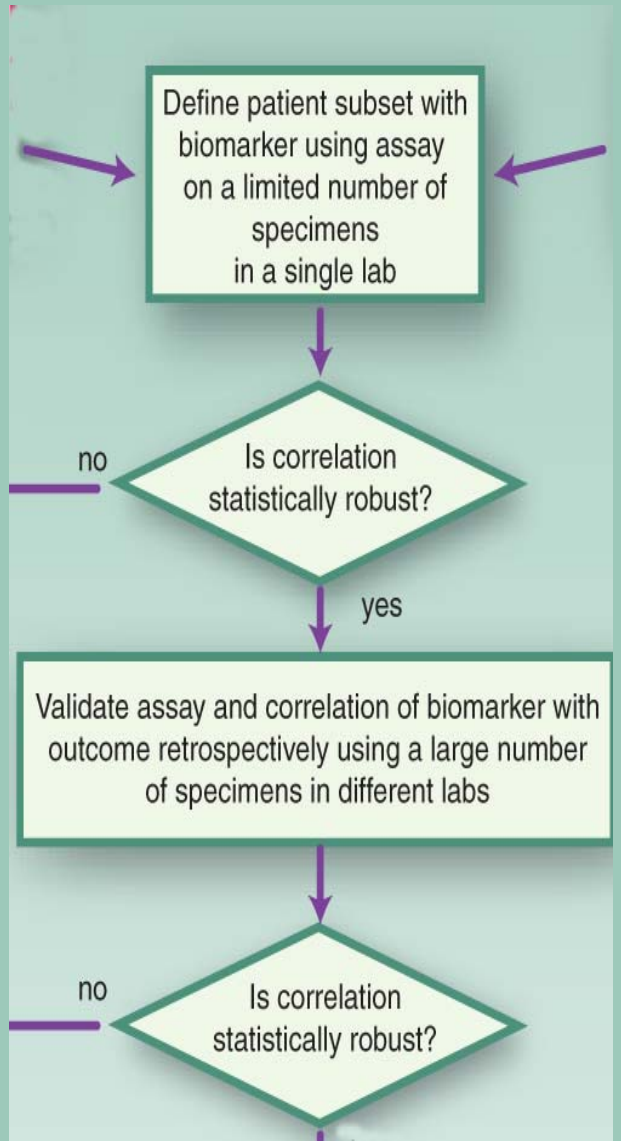
- ↑ 14-3-3ζ -> ↓ p53, ↑ TGFβ, ↑ EMT
- Confers resistance to anoikis *in vitro* (MCF10A in 3D)
- ↑ expression begins at ADH
- 14-3-3ζ ↑ in >40% of advanced breast cancers
- ↑ expression predicts poor patient survival

Biomarker Ki67, p16 & COX-2:
Credentialing: Scientific validation



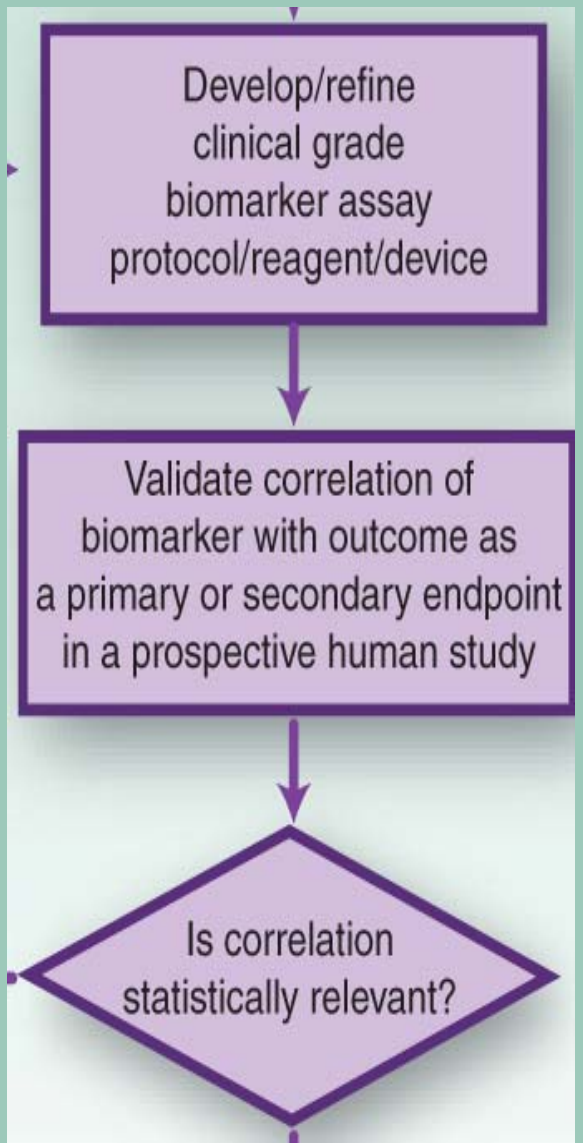
- Mechanistic studies of HMECs identify the Rb pathway as a key stress response regulator
- Associated with basal-like breast cancer
- ↑ Ki67, ↑ p16 and/or ↑ COX-2 proteins reflects abnormal response to cellular stress
- Abnormal stress response indicators predict recurrence as invasive cancer

Biomarker Pathway:
Creation of Modality



- What is the test?
  - Immunohistochemistry for 14-3-3ζ, p16, COX2, Ki67
- Validation in a retrospective study
  - Initial retrospective validation of p16, COX2, Ki67 complete
  - 14-3-3ζ starting
- Independent lab validation needed

Biomarker Pathway:
Preclinical Development



- Development of CLIA assay
- Prospective validation study

Biomarker Pathway:
Supporting tools: Samples, samples, samples

Identify or develop biospecimen repositories linked with outcomes data

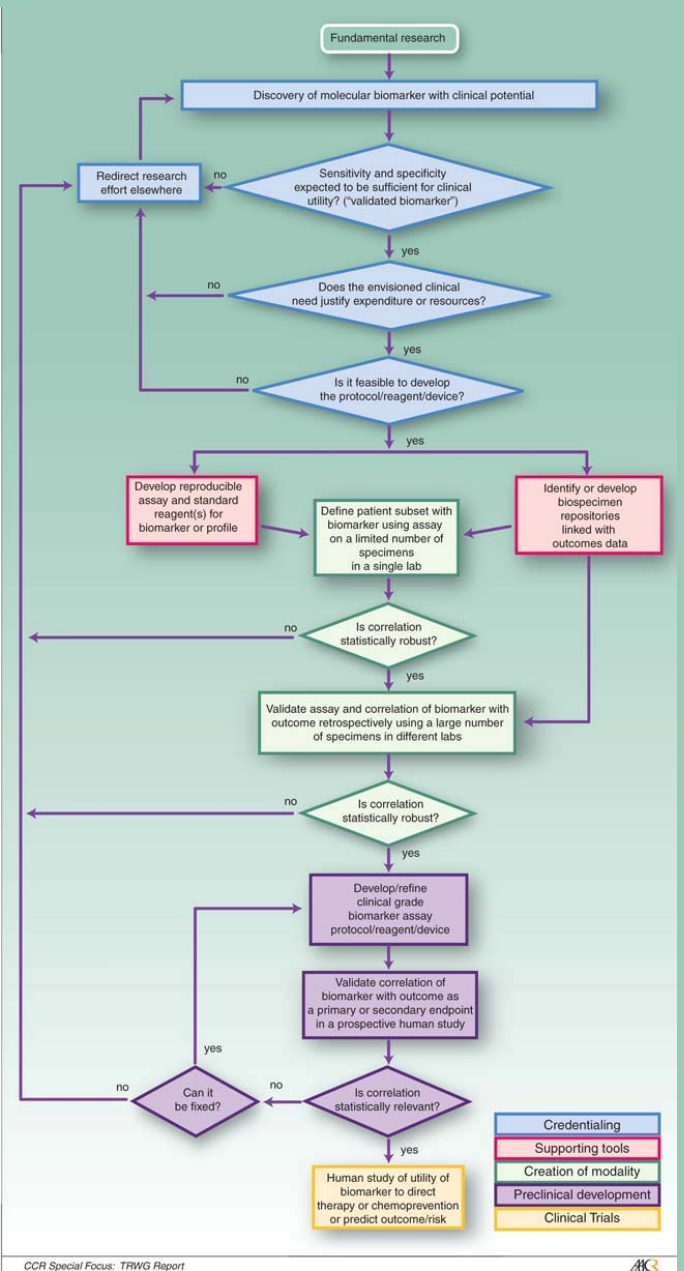
- Need retrospective DCIS tissue samples with 15 year follow-up!
- Samples are small
- Prospective validation study should start NOW

Biomarker Pathway:
Clinical Trials

Human study of utility of biomarker to direct therapy or chemoprevention or predict outcome/risk

- Need consortium for validation
  - Breast SPORES? EDRN? NCI?
  - Special consortium developed under STRAP mechanism?
  - Prospective validation will take an 15 years

Markers to predict subsequent events in women with early breast cancer



Need to be able to ID small fraction of DCIS patients that need aggressive treatment

14-3-3 ζ Ki67, p16, COX 2 promising biomarkers

Robust assays developed but not yet in independent labs or in CLIA format

Tissue samples needed for assay validation not readily available

Need to develop a consortium to validate markers — STRAP?